APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form):

SOTAN 75 mg (tablets)

SOTAN 150 mg (tablets)

SOTAN 300 mg (tablets)

COMPOSITION:

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Irbesartan is a specific antagonist of angiotensin II receptors (AT_1 subtype). Angiotensin II is an important component of the renin-angiotensin system and is involved in the pathophysiology of hypertension and in sodium homeostasis.

Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT_1 subtype) receptors localised on vascular smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT_1 receptor and a much greater affinity (more than 8 500 fold) for the AT_1 receptor than for the AT_2 receptor (a receptor that has not been shown to be associated with cardiovascular homeostasis).

Irbesartan does not inhibit enzymes involved in the renin-angiotensin system (i.e. renin, angiotensin converting enzyme [ACE]), or affect other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Irbesartan blockade of AT_1 receptors interrupts the feedback loop within the renin-angiotensin system, resulting in increases in plasma renin levels and angiotensin II levels. Aldosterone plasma concentrations decline following irbesartan administration, however, serum potassium

levels are not significantly affected (mean increase of < 0,1 mEq/l) at the recommended doses. Irbesartan has no notable effects on serum triglycerides, cholesterol or glucose concentrations. There is no effect on serum uric or urinary acid excretion.

Pharmacokinetic properties:

Irbesartan is an orally active medicine and does not require biotransformation for its activity. Following oral administration, irbesartan is well absorbed. The absolute oral bioavailability of irbesartan is 60 to 80 %. Food does not affect the bioavailability. Peak plasma concentration occurs at 1,5 to 2 hours after oral administration. Irbesartan is approximately 90 % protein-bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution is 53 to 93 litres.

In plasma, unchanged irbesartan accounts for 80 to 85 % of the circulating radioactivity following oral or intravenous administration of ^{14}C irbesartan.

Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (≈ 6 %). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme 2C9; isoenzyme 3A4 has negligible effect. It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with medicine metabolism (i.e. 1A1, 1A2, 2A6, 2B6, 2D6 or 2E1). Irbesartan does not induce or inhibit isoenzyme 3A4.

Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20 % of the administered radioactivity after an oral or intravenous dose of ^{14}C irbesartan is recovered in urine with the remainder in the faeces. Less than 2 % of the dose is excreted in urine as unchanged irbesartan.

The terminal elimination half-life ($t_{1/2}$) of irbesartan is 11 to 15 hours. The total body clearance of intravenously administered irbesartan is 157 to 176 ml/min, of which 3,0 to 3,5 ml/min is renal clearance.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation (< 20 %) is observed in plasma upon repeated once-daily dosing.

In elderly (male and female) normotensive subjects (65 to 80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentrations (C_{max}) of irbesartan are approximately 20 % to 50 % greater than those observed in younger subjects (18 to 40 years). Regardless of age, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed.

In black and white normotensive subjects, the plasma AUC and $t_{1/2}$ of irbesartan are approximately 20 to 25 % greater in blacks than in whites; the peak plasma concentrations (C_{max}) of irbesartan are essentially equivalent.

In patients with renal impairment (regardless of degree) and in haemodialysis patients, the pharmacokinetics of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan is not significantly altered.

INDICATIONS:

SOTAN is indicated for the treatment of essential hypertension.

It may be used either alone or in combination with other antihypertensive medicines.

SOTAN is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (> 300 mg/day) in patients with Type 2 diabetes and hypertension.

CONTRA-INDICATIONS:

SOTAN is contra-indicated in patients who are hypersensitive to irbesartan or to any other component of the **SOTAN** formulation.

A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.

Hereditary or idiopathic angioedema

Hypertrophic obstructive cardiomyopathy (HOCM)

Severe renal function impairment (creatinine clearance less than 30 ml/min)

Bilateral renal artery stenosis

Renal artery stenosis in patients with a single kidney

Aortic stenosis

Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **INTERACTIONS**).

Porphyria

Lithium therapy: Concomitant administration with **SOTAN** may lead to toxic blood concentrations of lithium (see **INTERACTIONS**).

Use of **SOTAN** with renin inhibitors such as aliskiren.

Paediatric Use:

Safety and effectiveness in paediatric patients have not been established.

Pregnancy and lactation

(See **WARNINGS AND SPECIAL PRECAUTIONS** and **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving **SOTAN**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See **CONTRA-INDICATIONS** and **PREGNANCY AND LACTATION**).

Hypotension – Volume-Depleted Patients:

SOTAN has been associated with hypotension in hypertensive patients without other co-morbid conditions. Symptomatic hypotension may be expected to occur in sodium/volume-depleted patients such as those treated vigorously with diuretics and/or salt restriction, or on haemodialysis. Volume and/or sodium-depletion should be corrected before initiating therapy with irbesartan or a lower starting dose (**SOTAN 75 mg TABLETS**) should be considered.

Hyperkalaemia:

May occur during the treatment with **SOTAN**, and especially frequent in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

Dual blockade of the RAAS with angiotensin-receptor blockers, ACE-inhibitors, or renin inhibitors such as aliskiren increases the risk of hypotension, hyperkalaemia and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients taking **SOTAN** and other medicines that affect the RAAS.

ACE inhibitors and angiotensin-receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

General:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g. hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with other medicines that affect this system has been associated with oliguria and/or progressive uraemia and with acute renal failure and/or death. The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist cannot be excluded.

Use in the elderly:

In clinical studies there was no age-related difference in efficacy or safety profile of **SOTAN.**

Effects on the ability to drive or use machinery:

SOTAN may cause side effects such as dizziness, headaches and nervousness which may impair concentration, therefore caution is advised until the effect of **SOTAN** on the individual is established.

INTERACTIONS:

Based on *in vitro* data, no interactions would be expected to occur with medicines whose metabolism is dependent upon cytochrome P450, isoenzymes 1A1, 1A2, 2A6, 2B6, 2D6, 2E1 or 3A4.

SOTAN is primarily metabolised by 2C9, however, during clinical interactions studies, no significant pharmacodynamic interactions were observed when **SOTAN** was co-administered with warfarin (a medicine metabolised by 2C9).

NSAIDs should be used with caution in patients taking **SOTAN** as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of NSAIDs may also attenuate the hypotensive effect of **SOTAN**.

Giving lithium with ACE inhibitors has been reported to increase serum-lithium concentrations, resulting in some cases, in lithium toxicity (see **CONTRA-INDICATIONS**).

Dual blockade of the RAAS with angiotensin-receptor blockers, ACE-inhibitors, or renin inhibitors such as aliskiren increases the risk of hypotension, hyperkalaemia and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAAS inhibitors concomitantly.

SOTAN does not affect the pharmacokinetics of digoxin or simvastatin.

The pharmacokinetics of irbesartan is not affected by co-administration with nifedipine or hydrochlorothiazide.

Based on experience with the use of other medicines that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium (see **CONTRA-INDICATIONS**).

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see **CONTRA-INDICATIONS**). When pregnancy is planned or confirmed **SOTAN** should be discontinued.

Medicines affecting the renin-angiotensin system, such as **SOTAN**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

DOSAGE AND DIRECTIONS FOR USE:

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food.

In patients insufficiently controlled with 150 mg once daily, the dose of **SOTAN** can be increased to 300 mg, or other anti-hypertensive agents can be added.

In patients with hypertension and type 2 diabetic renal disease, 300 mg of **SOTAN** once daily is the preferred maintenance dose.

Elderly Patients and Patients with Renal or Hepatic Impairment:

No dosage reduction is generally necessary in the elderly or in patients with mild to moderate impaired renal function or hepatic function.

Patients with Intravascular Volume Depletion:

See **WARNINGS AND SPECIAL PRECAUTIONS** – Hypotension – Volume-depleted patients.

SIDE EFFECTS:

The following side effects have been reported:

Immune system disorders

Less frequent:

Angioedema

Metabolism and nutrition disorders

Less frequent:

Hyperkalaemia.

Psychiatric disorders

Less frequent:

Anxiety and/or nervousness.

Nervous system disorders

Frequent:

Dizziness.

Less frequent:

Headache.

Ear and labyrinth disorders

Less frequent:

Tinnitus, vertigo.

Cardiac disorders

Less frequent:

Tachycardia.

Vascular disorders

Frequent:

Orthostatic hypotension, flushing.

Less frequent:

Hypotension usually seen in volume-or salt-depleted patients receiving high doses of a diuretic.

Respiratory, thoracic and mediastinal disorders

Less frequent:

Upper respiratory infection (cold symptoms), cough.

Gastrointestinal disorders

Frequent:

Nausea, vomiting.

Less frequent:

Diarrhoea, dyspepsia, dysgeusia.

Hepato-biliary disorders

Less frequent:

Jaundice, increased liver function tests, hepatitis.

Skin and subcutaneous tissue disorders

Less frequent:

Urticaria.

Musculoskeletal, connective tissue and bone disorders

Less frequent:

Musculoskeletal pain, arthralgia, myalgia, muscle cramps.

Reproductive system and breast disorders

Less frequent:

Sexual dysfunction.

General disorders and administrative site conditions

Frequent:

Fatigue.

Less frequent:

Chest pain

Investigations

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving therapy with **SOTAN.**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The patients should be closely monitored and treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage.

SOTAN is not removed from the body by haemodialysis.

IDENTIFICATION:

SOTAN 75 mg:

White to off-white biconvex oval shaped uncoated tablets debossed with ‘H 28’ on one side and plain on other side.

SOTAN 150 mg:

White to off-white biconvex oval shaped uncoated tablets debossed with 'H 29' on one side and plain on other side.

SOTAN 300 mg:

White to off-white biconvex oval shaped uncoated tablets debossed with 'H 30' on one side and plain on other side.

PRESENTATION:

SOTAN 75 mg / 150 mg / 300 mg

Blister Pack:

Tablets are packed in Clear 250 micron PVC film coated with 60 GSM PVDC and Printed 25 micron silver-grey Aluminium foil. Each blister contains 10 Tablets.

Pack size: **30's** – Each carton contains 3 blisters of 10 Tablets each.

HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE container of 33 mm neck finish with a white 33 mm – 400 RS closure with induction sealing wad containing Cotton coil, 9 gm/yard.

Each container contains 30 Tablets. Each HDPE container is enclosed in an outer cardboard carton.

Pack size: **30's -** One HDPE container contains 30 Tablets.

STORAGE INSTRUCTIONS:

Store in a dry place at or below 25 ℃.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

SOTAN 75 mg: 45/7.1.3/1051

SOTAN 150 mg: 45/7.1.3/1052

SOTAN 300 mg: 45/7.1.3/1053

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of registration:

29 July 2016

Date of revision:

24 November 2021